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# ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

## DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

### LEADING ARTICLES IN THIS NUMBER

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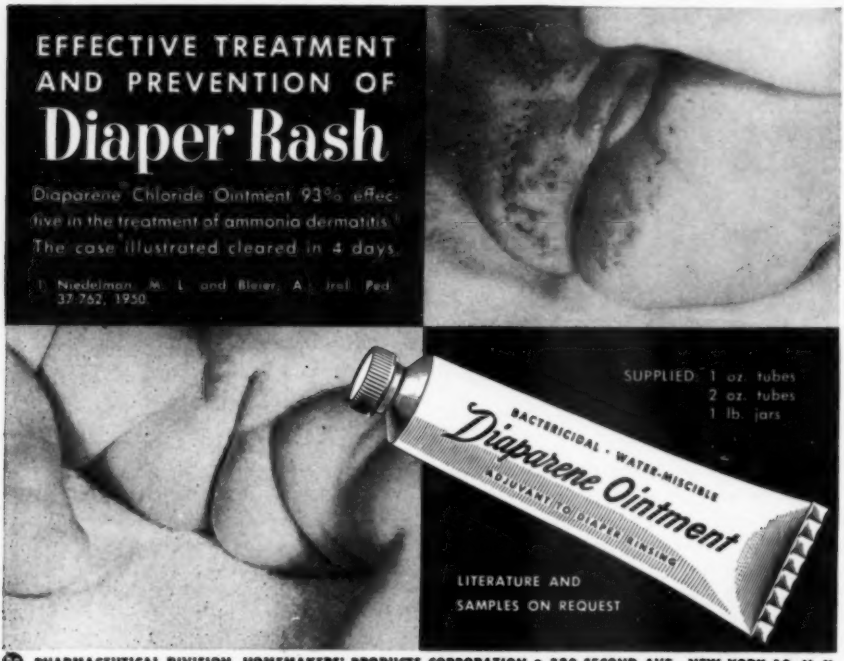
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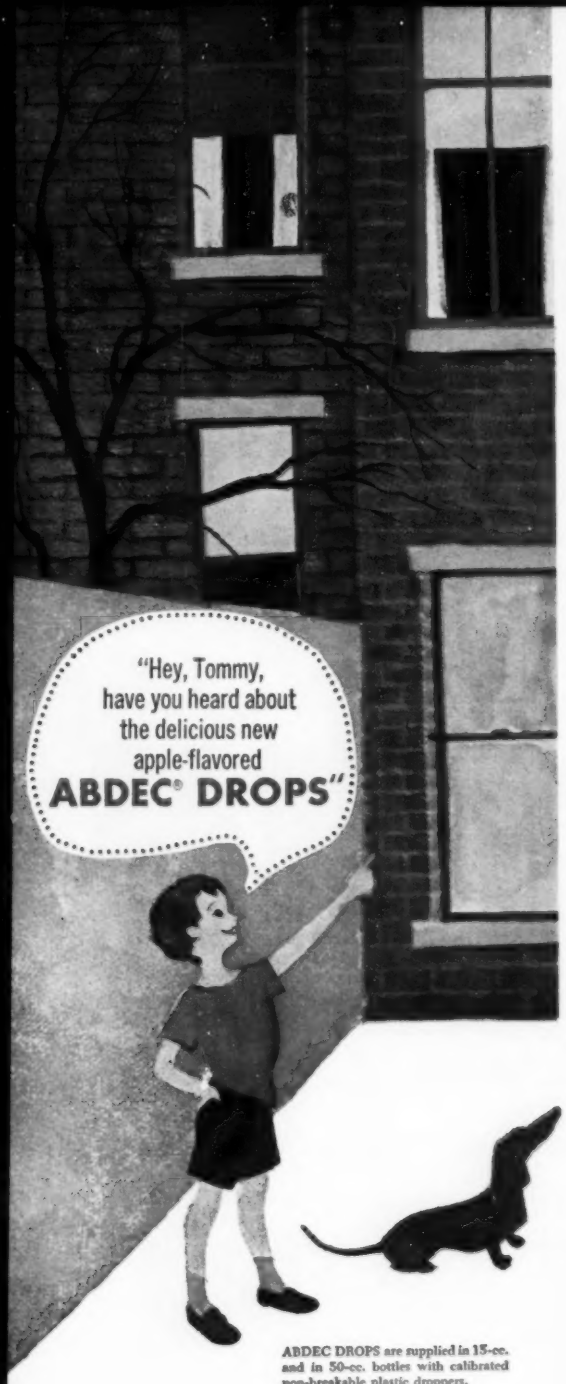


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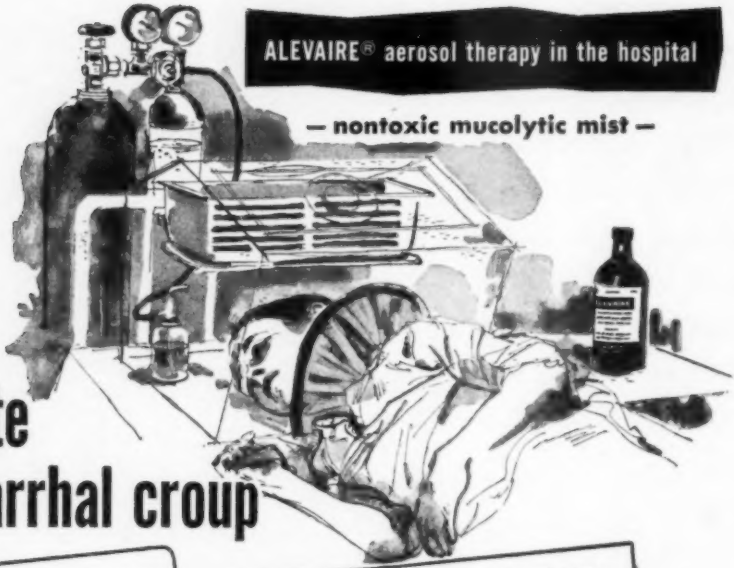

# acute catarrhal croup

**CASE REPORT***

D D., a 2 year old male with fever, cough and laryngeal stridor of one day's duration, was hospitalized because of continued respiratory distress. Treatment had consisted of penicillin, injections and wet vapor inhalations.

Auscultation on arrival revealed harsh breath sounds on both sides and coarse rhonchi. Continuous crouping cough caused severe respiratory distress; the pharynx was injected and the tonsils were large. Diagnosis was acute catarrhal croup.

The child was placed in a croup tent with a humidifier, and antibiotics were administered. The condition did not change and Alevaire aerosol was begun in the evening. The cough gradually became easier and less frequent. The next day he rested comfortably, his temperature was reduced, no respiratory distress was noted, and the lungs were almost clear on auscultation. A day later no further therapy was required and the child was discharged on the fourth day after admission.

*Smessaert, Andre; Collins, V.J.; and Kracum, V.D.: *New York Jour. Med.*, 55:1587, June 1, 1955.

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# TREATMENT OF CHRONIC ENURESIS, POOR WEIGHT GAIN, AND POOR APPETITE IN INSTITUTIONAL CHILDREN*

ALFRED J. VIGNEC, M.D.**
AUGUST MOSER, M.D.,
and
JUAN F. JULIA, M.D.
New York.

This is a study of the treatment of enuresis, poor weight gain and poor appetite in institutional children. The patients were carefully observed by the three authors and every attempt was made to control observations in order to give as objective a report as possible. For this reason three plans of treatment were used; one of internal control, one reversal of treatment and one with the test substance alone. Patients suffering from chronic diseases were excluded from the study. A total of ninety-two children were observed and the results seem to indicate that the test material used (Elixir Donnatal® Plus) was a useful adjunct to the treatment of enuresis and in instances of poor weight gain. It was felt, by the authors, that the plan used for study was not as successful in giving an objective appraisal where appetite was concerned as it was in the other two conditions studied. Nonetheless, it was useful in that it somewhat allayed tension in the mothers and the attendants who placed too much emphasis on appetite as a criteria of health.

* From the Department of Pediatrics New York Foundling Hospital and St. Vincent's Hospital, New York.
** Clinical Professor of Pediatrics, N. Y. U.-Bellevue Medical School, New York.
This study was aided by a grant from the A. H. Robins, Co., Inc., Richmond, Va.

## INTRODUCTION

Some of the most vexing problems with which the pediatrician must deal are those generally attributed to the hyperactive child and those children who are, to all intents and purposes, under severe emotional tension. These children or their parents present themselves with complaints that are heavily weighted with psychogenic factors such as enuresis, poor weight gain, poor appetite, chronic resistance to sleep, and a variety of social maladjustments. With institutional children, these problems are more severe for we are dealing with situational factors which are, at least for some time, irreversible. Most of these problems require primarily psychotherapeutic management of the child and those adults in his immediate environment, whether they be parents, foster parents, or attendants. Indeed, some of the best contributions to the field have been made by psychiatrists.[1,2] One of the difficulties in psychotherapeusis with children, however, is maintaining a good rapport with the child and his parents in the face of repeated failures and a prolonged persistence of symptoms. For this reason adjunct treatment even if it results in only partial immediate success is of considerable assistance.

Phenobarbital, because of its safety and range of usefulness, has been widely used in pediatric practice as a mild sedative and the belladonna group of alkaloids have been employed and recommended for their antispasmodic activity—particularly in the treatment of enuresis.[2,4] The B complex vitamins are particularly useful from a nutritional point of view in psychosomatic state. Since it would seem that a combination of these drugs would be particularly applicable to our available case material, a planned study of the effectiveness of this adjunct was instituted and serves as the basis of this report.

## METHODS AND MATERIAL

*Clinical Material.* The clinical material was comprised of institutional children in residency at St. Agatha's Home in Nanuet, New York and foster-home children who were under the pediatric supervision of the New York Foundling Hospital, New York City. All of these children are victims of broken homes and, as is to be expected, the incidence of psychogenic disturbances, maladjustments, and emotional difficulties is apt to be higher in this

group than that of children living in a normal home environment. Furthermore, and this is an important point, evidence of maladjustments had existed in this case material for some time prior to their inclusion in this study. In practically every instance these cases had been subject to other methods of treatment without success. These included various forms of medication, psychotherapy, and environmental alterations. None of the children included in the study were suffering from chronic diseases and, as a matter of fact, this group was specifically excluded from consideration. The children at Nanuet were observed weekly at the infirmary and were carefully evaluated by a qualified perdiatrician; at the New York Foundling clinic, weekly observations were not always possible because of transportation difficulties and school commitments. These children, however, were seen at least monthly.

A total of ninety-two children were introduced to the study with an age range of between 7 months and 14 years—the 5 year to 9 year age group predominating. There were sixty-six boys and twenty-six girls. Only those who had been observed for a period of at least one month on the test substance were subjected to statistical analysis. Consequently eighty-one cases were thought to have been studied comprehensively enough to be included in this report and eleven were dropped, seven of the latter because of incomplete data, and four for various causes which will be detailed later. The period of observation ranged from one to eight months with over 50 per cent of the cases being carefully followed for two to four month periods.

*Test substance, control and dosage.** The test substance consisted of Donnatal[R] Plus Elixir having the following composition, each 5 cc. containing:—

| | | |
|---|---|---|
| Phenobarbital (¼ gr.) | 16.2 | mg. |
| Hyoscyamine sulfate | 0.1037 | mg. |
| Atropine sulfate | 0.0194 | mg. |
| Hyoscine hydrobromide | 0.0065 | mg. |
| Thiamine HCL | 3.0 | mg. |
| Riboflavin | 2.0 | mg. |
| Nicotinamide | 10.0 | mg. |
| Ca pantothenate | 2.0 | mg. |
| Pyridoxine HCL | 0.5 | mg. |

* Test and control material supplied by the A. H. Robins Co., Inc., Richmond, Va.

The control substance was originally intended to serve as a placebo with none of the active ingredients of the test substance. It was found to be technically impossible, however, from a taste and appearance point of view, to devise a placebo which would meet these requirements. Accordingly, a control substance was incorporated in the study which contained all the active ingredients of the test material with the sole exception of phenobarbital. While this had the advantage of being practically indistinguishable from the test substance, it did have the obvious disadvantage of possible therapeutic effectiveness. The materials were distributed in such a manner that the actual ingredients and the identity of the two materials would not be known to the investigators or the users.

Since effective dosages might be expected to vary not only with age and weight but also with the intensity of the symptomatology, the study was initiated with a low dose schedule (one quarter of a teaspoonful three times a day of test substance) and increased until a clinically effective dose was reached in a preponderance of the cases. This was continued until an effective dosage plan was stabilized and it seemed satisfactory to adopt the following schedule:

| | |
|---|---|
| 1 - 3 years | ½ teaspoon, t.i.d. |
| 3 - 6 years | ½ - 1 teaspoon, t.i.d. |
| 6 years and up | 1 teaspoon, t.i.d. |

## PLAN OF STUDY

In order to make the greatest use of our material and to minimize subjective impressions, several plans of treatment were utilized. To some extent, we were aided in our attempts to obtain an objective appraisal of effectiveness by the fact that all the cases were children and consequently explanatory discussions could be eliminated—very few of the children, if any, knew what the medication was supposed to accomplish.

*Plan I:* The method used in this plan was that of intrasubject comparison.[6] Thirty-eight patients received a course of test substance for at least one month, a course of control substance for one month, followed by another course of test substance for at least one month.

*Plan II:* Twenty-seven patients were given a course of test substance only for a minimum of one month. It might be noted

that this group of patients also served to adjust our dosage schedule.

*Plan III:* This was a reversal of treatment method. Sixteen children were initiated into the study with a course of the control substance for a minimum of one month and this was followed by a course of test material.

## RESULTS

Our case material was devisible into two groups. One group was comprised of patients who presented themselves with only one of three major complaints—enuresis, poor weight gain, or poor appetite. The second group had an overlapping of these major complaints, such as enuresis and poor weight gain, or, in addition to one of the major complaints, evidence of maladjustment such as difficulties at school, emotional upsets, or anti-social behaviour. It was necessary, therefore, to include the same children under different groupings in the results so that our analysis is actually a study of the effectiveness of the medication on various categories of symptom complex. Since it is our feeling that a multiplicity of symptoms might have a direct relationship to the severity of the problem, and hence be more difficult to treat, the results of these two groups were tabulated separately.

*Enuresis.* All cases representing instances of nocturnal enuresis were resident at St. Agatha's Home in Nanuet, New York, and it must be borne in mind that the condition had been present for a long period of time. There was a total of forty-four cases, thirty-eight boys and six girls. The incidence in the institution was 10.3 per cent, the rate among boys being 16.5 per cent and in girls three per cent. This data correlates with most estimates of the incidence of this condition, 5 per cent to 15 per cent, and confirms the generally accepted opinion that it is more frequent in boys than in girls. The girls were under the direct care of Sisters or lay women so that it was not likely that timidity or shyness would have deterred a report from being submitted. Moreover, the institutional environment would make concealment of this problem difficult at best.

Table I tabulates the results obtained under the different plans of treatment and a study of this table indicates that the test material produced rather consistent results and that these results did not seem to vary between the two groups—those with only enu-

resis as a presenting complaint and those with enuresis plus other complaints. Twenty patients were studied under Plan I (test period—control period—test period), and there were eight successes, two partial successes, and ten failures in both test periods. During the control period, there were five successes, one partial success, and fourteen failures.

TABLE I

TREATMENT OF ENURESIS

| | TEST MATERIAL | | | CONTROL | | | TEST MATERIAL | | |
|---|---|---|---|---|---|---|---|---|---|
| | S | P-S | F | S | P-S | F | S | P-S | F |
| PLAN I | | | | | | | | | |
| ENURESIS | | | | | | | | | |
| 1) alone | 4 | 1 | 6 | 2 | — | 9 | 4 | 1 | 6 |
| 2) plus other symptoms | 4 | 1 | 4 | 3 | 1 | 5 | 4 | 1 | 4 |
| Totals | 8 | 2 | 10 | 5 | 1 | 14 | 8 | 2 | 10 |
| PLAN II | | | | | | | | | |
| ENURESIS | | | | | | | | | |
| 1) alone | 2 | — | 4 | | | | | | |
| 2) plus other symptoms | 2 | 1 | — | | | | | | |
| Totals | 4 | 1 | 4 | | | | | | |
| PLAN III | | | | | | | | | |
| ENURESIS | | | | | | | | | |
| 1) alone | | | | — | — | 13 | 1 | — | 12 |
| 2) plus other symptoms | | | | — | — | 2 | — | — | 2 |
| Totals | | | | — | — | 15 | 1 | — | 14 |

S—cessation of enuresis
P-S—reduction in frequency
F—no result

Nine patients were observed under the second plan of treatment and the results, as indicated in Table I, were consistent with those obtained with the test periods of Plan I, there being four success, one partial success, and four failures.

Fifteen patients were treated by Plan III. With this method, the patients were first treated with the control substance and then

were given a course of test material. The control failed to initiate a single successful or partially successful result in fifteen instances, Table I. There was one instance of success in the test course that followed.

*Poor Weight Gain.* Seventy children were treated for poor weight gain, twenty-five girls and forty-five boys. The criteria of poor weight gain was either failure to gain over a period of

TABLE II

TREATMENT OF POOR WEIGHT GAIN

| | TEST MATERIAL | | | CONTROL | | | TEST MATERIAL | | |
|---|---|---|---|---|---|---|---|---|---|
| | E | S | F | E | S | F | E | S | F |
| PLAN I | | | | | | | | | |
| POOR WEIGHT GAIN | | | | | | | | | |
| 1) alone | 1 | 1 | 1 | — | — | 3 | — | 1 | 2 |
| 2) plus other symptons | 1 | 18 | 13 | — | 7 | 25 | 5 | 8 | 19 |
| Totals | 2 | 19 | 14 | — | 7 | 28 | 5 | 9 | 21 |
| PLAN II | | | | | | | | | |
| POOR WEIGHT GAIN | | | | | | | | | |
| 1) alone | — | 1 | — | | | | | | |
| 2) plus other symptoms | 2 | 10 | 6 | | | | | | |
| Totals | 2 | 11 | 6 | | | | | | |
| PLAN III | | | | | | | | | |
| POOR WEIGHT GAIN | | | | | | | | | |
| 1) alone | | | | — | — | — | — | — | — |
| 2) plus other symptoms | | | | — | 4 | 12 | 1 | 10 | 5 |
| Totals | | | | — | 4 | 12 | 1 | 10 | 5 |

E—Weight gain better than 240 gms. monthly
S—Weight gain between 120-240 gms. monthly
F—no gain, or loss

time, generally several weeks, or loss of weight. An outstanding feature of these patients was that poor weight gain rarely appeared alone as a complaint, but was practically always associated with other complaints or evidence of maladjustment, Table II.

The method of treatment of Plan I was followed in thirty-five

cases and it is apparent that a disparity existed between the two test courses. In the first test period, there were two excellent results, nineteen satisfactory results, and fourteen failures, Table II. After an interval of control medication, the test material produced five excellent results, nine satisfactory results, and twenty-one failures. There was a spread in both directions towards more excellent results, but also towards more failures. The control material produced seven satisfactory results and twenty-eight failures.

Nineteen patients were treated with test material only (Plan II) and the distribution of results correlated with those of the first test period with two excellent, eleven satisfactory, and six failures, Table II.

TABLE III

TREATMENT OF POOR APPETITE

| | TEST MATERIAL | | | CONTROL | | | TEST MATERIAL | | |
|---|---|---|---|---|---|---|---|---|---|
| | S | E | F | S | E | F | S | E | F |
| PLAN I | | | | | | | | | |
| POOR APPETITE | | | | | | | | | |
| 1) alone | 1 | — | — | 1 | — | — | 1 | — | 1 |
| 2) plus other symptoms | 13 | 1 | — | 9 | 1 | 4 | 13 | 1 | — |
| Totals | 14 | 1 | — | 10 | 1 | 4 | 14 | 1 | — |
| PLAN II | | | | | | | | | |
| POOR APPETITE | | | | | | | | | |
| 1) alone | — | 4 | 5 | | | | | | |
| 2) plus other symptoms | — | — | — | | | | | | |
| Totals | — | 4 | 5 | | | | | | |

S—definite improvement
E—equivocal
F—failure

Plan III method of treatment produced four satisfactory results with the control substance and twelve failures. The test material produced one excellent result, ten satisfactory and five failures. In this group of patients, results obtained with the initial courses of test material was consistent under all three plans of treatment, Table II.

*Poor Appetite:* While observations on appetite were made on almost all patients in the study, many of these were invalidated

by subjective elements which could not be dissociated for accurate information or recording. It was noteworthy that, in our experience, poor appetites were practically never a complaint made by the children but most frequently that of their mothers or attendants.

The effects on appetite of the test material and the control on twenty-four children are recorded in Table III. Fifteen children were observed under Plan I method of treatment and nine under Plan II. The results were identical in both test periods with fourteen showing definite improvements, one equivocal, and four failures. The validity of the results obtained during the test periods under Plan I are questionable when viewed in the light of our findings with nine patients receiving test material alone, Table III. Here it will be noted there were four equivocals and five failures.

*Side Effects.* There were two hundred and eight courses of test material given and one hundred and one courses of control substance. No side reactions were observed with the control and four were noted with the test material and, while the latter were not severe, medication was discontinued in each instance. One child objected strenuously to taste and one vomited repeatedly when the medication was introduced. One ten year old boy developed blurring of vision after three days of medication. One seven year old girl developed a fine erythematous rash over the trunk which disappeared on discontinuation of the drug and reappeared when the medication was readministered.

Table IV presents a summary of the results by courses.

## DISCUSSION

One of the most interesting developments in this study were the observations on enuresis. This condition in a chronic form, the type most frequently encountered in this study, is extremely difficult to manage. The very multiplicity of treatments advocated is evidence enough of the complexity of the problem.[1,2,7,8,9] Before entering this study, our patients previously had been managed by a variety of methods, such as a reward system, restriction of fluids after supper, awakening after the first sleep, etc. No medications had been used, however, and it was obviously impractical in an institutional environment to use a conditioned reflex method.[8] Traditionally, belladonna derivatives, atropine in particular, have been recommended as an adjunct to treatment[2,4] the pharma-

cological explanation being that these drugs may inhibit excessive detrussor tonicity.[4] It was apparent in our experience that the combination of mild sedation and the belladonna derivative were superior in effectiveness to the belladonna group alone, Table IV. The latter, in our reversal of treatment plan, were ineffective although by the intrasubject comparison method it was apparent that once success was achieved with the test material, the belladonna derivatives were able in some measure to sustain this success, Table I. The inability of the test material to produce a greater degree of success after the failure of the control might well highlight a point already referred to—the importance to the individual of some concrete evidence of progress. Another feature of the management of enuresis was undoubtedly the regular weekly visits to the pediatrician which had not been a feature of our previous methods of management. In the past, the problem had been handled through the attendants. The significance of this frequent contact with the pediatrician is obscure since patients under test and control material participated in this part of the program.

Efforts to induce an improvement in weight gain with the test material showed definitely more success than with the control, Table IV. This group of children were in general overactive and highly emotional, and furthermore, many of them were unaccustomed to a diet which, because of their racial and familial backgrounds, was deficient in spices and condiments. All of them in the past received, as a supplement to their diet, adequate vitamins without any observed effects. It could be properly assumed that the relaxation of tension states by the mild sedative and antispasmodic drugs in addition to vitamin B complex produced the the desired result. This has previously been reported in comparable adult states.[5]

Observations on appetite are extremely difficult to analyse in children. As we previously mentioned, this complaint was most frequently one made by the mothers or attendants. All too often we had the definite impression that the reporting on the part of the children evidenced a desire to please rather than any conviction on the part of the individual. One case in particular, we recall, where the mother's concern over poor weight gain and appetite almost completely disappeared when the child was introduced to the study. This mother was voluble in her endorsement of both materials, the child was noncommital, and the weight

remained stationary for weeks. We could in the analysis of our data establish no correlation, for example, between weight gain and appetite reporting. Psychological bias undoubtedly played a part in case finding and this inevitably led to sample bias. The cases which came to our attention were presented to us because the mothers or attendants were particularly concerned with appetite as an index of health. The observations, however, are not by any means entirely useless for they reflect success in the management of this symptom on the part of the child and the parent or attendant. Both materials proved highly successful in treating children with poor appetite, the test material showing slight superiority over the control substance, Table IV.

## SUMMARY

In the treatment of chronic, nocturnal enuresis in a group of institutionalized children, a test material containing a mild sedative, belladonna alkaloids and vitamin B complex (Elixir Donnatal® Plus) was effective in 41.7 per cent of instances. The same medication was successful in 56.2 per cent of instances in the management of children with poor weight gains and in a large number of instances (87 per cent) it produced a satisfactory result in the improvement of appetite.

TABLE IV

SUMMARY OF RESULTS
by
COURSES

| | TEST MATERIAL | | CONTROL | |
|---|---|---|---|---|
| | Number of Courses | Percent Effective† | Number of Courses | Percent Effective† |
| ENURESIS | 64 | 41.7 | 35 | 17.2 |
| POOR WEIGHT GAIN | 105 | 56.2 | 51 | 21.4 |
| POOR APPETITE | 39 | 87.†† | 15 | 73.3†† |

† Effective—complete or partial success
†† Equivocal results excluded

## CONCLUSION

Elixir of Donnatal® Plus is a useful adjunct in the treatment of chronic, nocturnal enuresis, poor weight gain and poor appetite when these symptoms appear in institutionalized children.

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FRACTURES OF THE UPPER EXTREMITY IN CHILDREN. J. C. Ivins. Minnesota Med., 38:296-298, May 1955. A plea is made for conservatism in treating fractures in children. The heavy periosteum that surrounds the bone in children may help to prevent displacement. Most of the time it makes for satisfactory manipulation and easier closed reduction. Nature will do a wonderful job in healing these fractures and normal function will be restored, as a rule, if physicians will simply assist nature to the extent of restoring alignment and providing proper immobilization for an adequate length of time. Thus completely satisfactory results can be obtained by traction or by closed manipulation and immobilization in plaster. Certain epiphysical injuries at the elbow may require open reduction when the aponeurosis is completely torn and the condylar fragment is rotated completely out of the joint and turned upside down or when avulsion of the internal epicondyle is associated with complete outward displacement of the elbow and frequently with damage to the ulnar nerve. The head of the radius in children must never be excised; in case of marked displacement of the upper radial epiphysis a short incision may be necessary to restore the parts under direct vision, and a Kirschner wire can be introduced from the back of the elbow through the capitellum into the shaft of the radius to hold its position for two or three weeks until early formation of callus occurs. —*J.A.M.A.*

# COMPARATIVE EVALUATION OF POWDERED WHOLE MILK (KLIM) WITH EVAPORATED MILK

HARRY R. LITCHFIELD, M.D., F.A.C.P.*
BROOKLYN.

For over a quarter of a century a dried milk powder (Klim)** has been successfully used in infant feeding. In many instances it has even replaced fresh cow's milk in household use. Holt and McIntosh[1], Amic[2] and others relate the advantages of powdered whole milk in infant feeding. In fact, Holt and McIntosh[1] used it routinely in the infants' ward of Johns Hopkins Hospital for a number of years. They stated that "in warm climates and when facilities for proper refrigeration are lacking, the use of dry milk greatly diminishes the risk of bacterial contamination." Dried milk is fundamentally cow's milk from which the water has been removed. The replacement of the water in making the formula restores the milk to its original state and nutritive value. The process in drying does not alter any of the components in any way as to reduce their value, and additional water may be used to dilute and modify the milk. In our comparative study it has been found to be an excellent infant formula. There are many reasons for this. First, the fat of fresh cow's milk is not injured by the drying process, the process, in fact, favors digestibility. Second, the sugar lactose is unaltered. Lactose is the physiological sugar, just as in mother's milk. Lactose is necessary to produce the formation of bifidus flora in the infant's intestine. This "biological reaction" is of utmost importance to the growth of the infant. Third, the proteins are rendered more digestible, the lactalbumin is not coagulated; and fourth, the vitamins are unimpaired to any extent.

Klim is an amorphous pale yellow powder with a milky odor. It represents the solids of fresh whole cow's milk with added vitamin D. Only the water is removed. Upon liquefaction with water, Klim becomes milk again.

The chief advantages in the use of Klim lie in (a) its easier digestibility; (b) its low bacterial count; (c) the convenience in making fresh formula whenever required; (d) the fact that carbo-

* Director of Pediatric Department at Brooklyn Womens Hospital, and at East New York Dispensary; Sr. Attending Pediatrician, Beth-El Hospital, Brooklyn, New York.
** Klim, the dry milk powder was supplied for this study by The Borden Co.

hydrates may be safely added to Klim to increase the CHO content.

APPROXIMATE COMPOSITION

| | Powder | Liquefied |
|---|---|---|
| Milk Fat | 28.0% | 3.3% |
| Milk Protein | 26.5 | 3.2 |
| Milk Sugar (Lactose) | 37.7 | 4.5 |
| Milk Minerals | 5.8 | .7 |
| Water | 2.0 | 88.3 |

CALORIC VALUE: per ounce 145.; per gram 5; per packed tablespoonful 40.

The latter facts were corroborated by Pritchard[3], Hess[4], Drummond[5], and, Hooker and Johnson[6].

Fresh whole milk is a good source of vitamin A, B, and G, and a fair source of vitamin C. Of these vitamins, A and G are relatively heat resistant and it is now generally acknowledged that there is no reduction of these factors in Klim as a result of the drying process[7].

The natural vitamin D content of cow's milk is low. Klim, however, has been fortified with 400 International Units of vitamin D per quart (425 I.U. per liter). This amount is considered ample from the nutritional point of view. The form of vitamin D is irradiated 7-dehydrocholesterol (vitamin $D_3$) and is completely tasteless.

Ashton[8], from his study, expressed the opinion that powdered milks can be fed safely to infants and that the development curve varies little from that of the normal breast fed infant.

METHOD OF STUDY

This study was designed to determine the nutrition, usefulness and comparative value of Klim and Evaporated Milk in infant feeding from a practical clinical basis. The investigation was carried out in a large, well conducted, obstetrical institution where close to 2800 newborns are delivered yearly. The patients were followed through the out-patient clinic of the hospital and a nearby local dispensary.

For the purpose of this study the infants were divided into two groups:

Group I (55 infants) include infants fed on Klim.

Group II (51 infants) include infants fed on Evaporated Milk.

We had a total of ninety-one infants on Klim, but only fifty-five had completed records for a six month period. There were one hundred and six infants started on Evaporated Milk formula but fifty-one infants had the full six months completed. The caloric intake of both groups was approximately the same.

The following is a schedule of the formulas and the time intervals when the formulas were changed:

SCHEDULE OF FORMULAS

| KLIM | EVAPORATED MILK |
|---|---|
| *In-Patient* | |
| 6 level tablespoons Klim | 6 ounces Evaporated Milk |
| 18 ounces boiled water | 12 ounces boiled water |
| 1 level tablespoon carbohydrate | 1 level tablespoon carbohydrate |
| *Discharge Formula* | |
| 10 level tablespoons Klim | 10 ounces Evaporated Milk |
| 24 ounces boiled water | 14 ounces boiled water |
| 1 level tablespoon carbohydrate | 1 level tablespoon carbohydrate |
| *Three Weeks* | |
| 12 level tablespoons Klim | 12 ounces Evaporated Milk |
| 24 ounces boiled water | 12 ounces boiled water |
| 2 level tablespoons carbohydrate | 2 level tablespoons carbohydrate |
| *Two Months* | |
| 13 level tablespoons Klim | 13 ounces Evaporated Milk |
| 26 ounces boiled water | 13 ounces boiled water |
| 2 level tablespoons carbohydrate | 2 level tablespoons carbohydrate |

*Remark:* Thereafter the infants were fed according to the progress of the child.

Both groups received the same amount of vitamins (Fortified Vi-Syneral) .3 cc. for in-patients and after one month .6 cc. throughout the period of study.

SUMMARY OF DATA OF PATIENTS ON KLIM

Birth to Six Months

1. Total number of infants - 55:
   Full term: 51-92%
   Premature: 4-8%
2. Morbidity.
   a. Conditions resulting from prenatal influences:
      Mongoloid—1
      Tight anal spinchter—1
      Cleft palate—1
      Congenital heart—1
      Jaundice—1
   b. Conditions resulting from intranatal influences:
      Cephalhematomas—3
   c. Conditions resulting from postnatal influences:
      Pharyngitis—1
      Diaper rash—1
3. Rh negative mothers—1
4. Stools - (stools recorded for 55 infants):

| No. of Stools | No. of Patients |
|---|---|
| 1 | 7 |
| 1-2 | 40 |
| 2-3 | 8 |
| 3 plus | 0 |

5. Excoriated buttocks - 1
6. Breast fed: 1—one day only
7. Number of infants receiving vitamins: 55
8. Number of cases discharged at end of one month: 2
   a. Mongoloid
   b. Cardiac anomaly.

SUMMARY OF DATA OF PATIENTS ON EVAPORATED MILK

Six Months

1. Total number of infants:—51
   Full term: 49—96%
   Prematures: 2—4%

2. Morbidity.
   a. Conditions resulting from prenatal influences:
      Tremors of newborn—calcium deficiency—1
      Rectal polyp—1
      Jaundice—2
   b. Conditions resulting from intranatal influences:
      Caput succedaneum—absorbed 8th day—1
   c. Conditions resulting from postnatal influences:
      Stomatitis—1
      Pylorospasm—1
      Diaper rash—7
      Loose stools—5
3. Rh negative mothers—7
4.

| No. of Stools | No. of Patients |
|---|---|
| 1 | 1 |
| 2 | 27 |
| 2-4 | 6 |
| 3 | 15 |
| 3-6 | 2 |

5. Excoriated buttocks—4
6. Breast feeding—2
7. Number of infants receiving vitamins—51
8. Number of cases discharged before 6 months—none.

The difference in the value of the two milk formulas were measured by the following methods:

(a) the average weight at different periods of the infant's life.

(b) the incidence of stools and excoriated buttocks and other factors resulting from postnatal influences.

Comparative summaries of data on weight curve, morbidity and other factors are as follows:

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COMPARATIVE STUDY OF KLIM VS. CONTROL

Fig. 1. "A" represents group of 55 infants fed on "Klim". "B" represents group of 51 infants who received control milk feeding. The table shows the total combined weight for each group from birth through the six months' period.
A mean (average weight) was established for both groups for each period by dividing the total weight by the number of infants in the group.
Also, the differences between the two means were established for each period and are indicated on the table.

Fig. 2. represents in graphic form the growth curve, in pounds, for group "A" (Klim) versus group "B" (control).

Fig. 3. is a graph showing the difference, in ounces, between the mean (average weight) for group "A" (Klim) and the mean for group "B" (control).

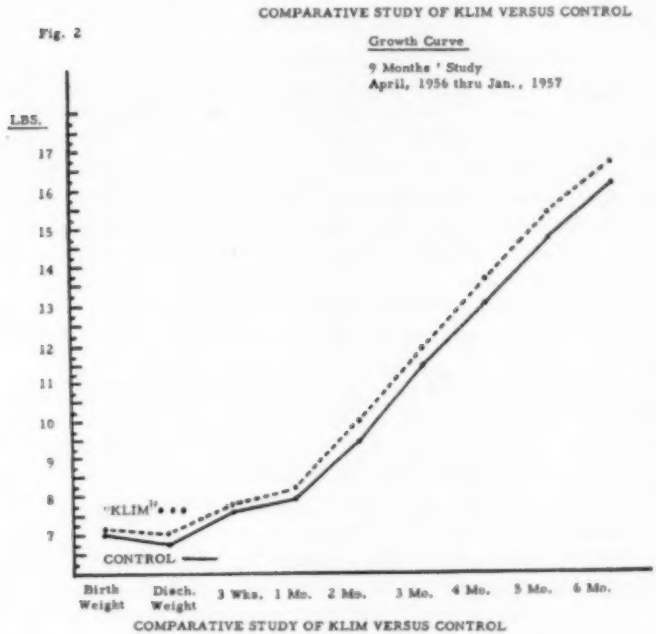
COMPARATIVE STUDY OF KLIM VS. CONTROL

Fig. 1

DR. LITCHFIELD - BROOKLYN WOMEN'S HOSPITAL
GROUP "A" - "KLIM"
GROUP "B" - CONTROL MILK FEEDING

| | | BIRTH WEIGHT | | DISCHARGE WEIGHT | | 3 WEEKS | | 1 MONTH | | 2 MONTHS | | 3 MONTHS | | 4 MONTHS | | 5 MONTHS | | 6 MONTHS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CODE | | | | | | | | | | | | | | | | | | |
| NUMBER | | 55 | | 55 | | 55 | | 54 | | 53 | | 53 | | 53 | | 53 | | 53 | |
| | | LBS. | OZ. | LBS. | OZ | LBS. | OZ. | LBS. | OZ | LBS. | OZ. | LBS. | OZ. | LBS. | OZ | LBS. | OZ | LBS. | OZ. |
| GROUP A TOTALS | | 392 | 14 | 386 | 10 | 627 | 11 | 438 | 0 | 527 | 0 | 621 | 14 | 719 | 3 | 809 | 0 | 882 | 5 |
| AVERAGES | | 7 | 2.26 | 7 | 048 | 7 | 12.48 | 8 | 1.75 | 9 | 15.04 | 11 | 11.68 | 13 | 9.12 | 15 | 4.16 | 16 | 10.40 |
| | | | | | | | | | | | | | | | | | | | |
| NUMBER | | 51 | | 51 | | 51 | | 51 | | 51 | | 51 | | 51 | | 51 | | 51 | |
| | | LBS. | OZ. | LBS. | OZ | LBS. | OZ | LBS. | OZ | LBS. | OZ | LBS. | OZ | LBS. | OZ. | LBS. | OZ. | LBS. | OZ. |
| GROUP B TOTALS | | 359 | 13 | 346 | 8 | 389 | 8 | 405 | 9 | 491 | 10 | 577 | 13 | 664 | 6 | 750 | 5 | 823 | 2 |
| AVERAGES | | 7 | 0.96 | 6 | 12.80 | 7 | 10.24 | 7 | 15.20 | 9 | 10.26 | 11 | 5.28 | 13 | 0.48 | 14 | 11.35 | 16 | 2.24 |
| | | | | | | | | | | | | | | | | | | | |
| DIFFERENCES A - B | | | 1.28 | | 3.68 | | 2.24 | | 2.55 | | 4.80 | | 6.40 | | 8.64 | | 8.80 | | 8.16 |
| | | | | | | | | | | | | | | | | | | | |
| DIAPER RASH | | | | | | | | | | | | | | | | | | | |
| GROUP "A" | 1.8% | | | | | | | | | | | | | | | | | | |
| GROUP "B" | 13.7% | | | | | | | | | | | | | | | | | | |

Fig. 2



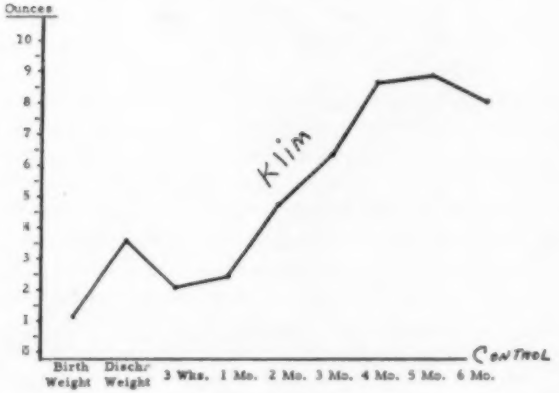




Fig. 3 - Difference between mean (average weight) of Klim-fed infant compared to mean of infant on control milk feeding from date of birth through six month period.

## CONCLUSION

This study was undertaken to determine the comparative value of Klim (The Borden Co.) and evaporated milk in infant feeding from a practical clinical basis. For purpose of study the cases were divided into two groups. Group I included ninety infants on Klim, of which fifty-five had completed a full six months study. Group II (control) included one hundred and six infants on evaporated milk, fifty-one of which completed six months of study. The caloric intake of both groups was approximately the same as indicated on page 133.

All measurements were subjected to statistical analysis (IBM), but in order to conserve space, only the summaries and graphs are shown.

The differences in the value of the two milks were measured by the following methods. The total combined weight for each group from birth through the six months period. Then a mean (average weight) was established for both groups for each period by dividing the total weight by the number of infants in the group. This is well illustrated in Figure 1.

A growth curve, in pounds, for Group I (Klim) versus Group II (Control) is graphically represented in Figure 2.

The difference in ounces between the mean (average weight) from birth through the six month period is graphically shown in Figure 3.

In the morbidity study a very significant finding was that the infants on Klim had 1.8 per cent diaper rash, whereas the control group on evaporated milk had 13.7 per cent involvement of diaper rash of the buttocks.

From our study we found the use of Klim advantageous because of its easier digestibility, low bacterial count, and convenience in making fresh formula. Furthermore, carbohydrates may be added according to the doctor's discretion. Lastly, it is obvious from the above charts that the weight curve of the infants on Klim showed a better weight gain than those on the control (evaporated milk).

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*60 Plaza Street.*

# CLINICAL REVIEW

*In order to encourage the writing of clinical articles by recent graduates or senior medical students, the* ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Lawrence B. Slobody, at New York Medical College, New York, and Doctor Walsh McDermott, at Cornell Medical School, New York. Other interested medical schools are cordially invited to submit student papers for consideration.*

## HYPERVITAMINOSIS A*

ROGER C. BRESLAU
New York.

"It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future."

Willian Osler—Gulstonian Lectures, 1885.

For many years it has been known that excessive intake of vitamin A would produce toxic effects in small animals, but not until Joseph's report[1] in 1944 was the cornerstone laid for recognition of the symptom complex in man. Because the majority of the subsequent reports on this condition have appeared either in pediatric or roentgenological journals, practitioners in general may be unaware of the need for recognizing the syndrome of hypervitaminosis A, which is readily reversible once it is diagnosed. Its diagnosis should not be difficult with a "high index of suspicion," since in most cases it exhibits fairly distinctive clinical and radiographic findings.

Although the picture of hypervitaminosis A may not be generally known as yet to clinicians, there are sufficient reports and experimental data for one to consider it a well-established and characteristic syndrome. The yearly increase in the number of reports on the condition indicate that many cases may have been overlooked in the past. Prompted by a new display of interest in the condition, prominent journals on both sides of the Atlantic have featured editorials on the subject,[2] and its inclusion for the first time in standard American medical textbooks[3] will doubtlessly lead to a more general recognition of this symptom complex by the future practitioner.

* Submitted as partial fulfillment of the requirements of the course from the classes of Dr. Walsh McDermott at the Cornell University Medical College, New York.

Because of the popular belief that vitamin preparations may be taken indiscriminately, and that amounts far above those present in the diet are needed for good health, it is surprising that the medical profession sees so few cases of toxicity due to overdosage. The previous paucity of reports on the occurrence of the syndrome, in the opinion of Fried and Grand,[4] was probably due to lack of recognition rather than to lack of actual incidence. At the annual meeting of the American Pediatric Society in 1949, a distinguished investigator in vitamin research, the late J. M. Lewis, stated that in the United States there are possibly more individuals with hypervitaminosis A than with vitamin A deficiency.[6]

It is only with the development and widespread marketing of extremely high potency vitamin concentrates that it has become possible to readily induce vitamin A intoxication in human beings, either through zealous overdosage without the advice of a physician, or through misinterpretation of such advice. In the press and over the radio, and through every medium of advertising comes the message about the relationship between high vitamin intake and improved vitality, increased resistance to infection, or accelerated recovery from illness. Vitamin sales records[8] bear out the fact that these exhortations do not go unheeded, and not infrequently, through "superenthusiasm," enormous amounts of concentrated vitamin A are taken by an adult, or administered to an infant or a young child resulting in serious injury.

It is proposed to present arguments in favor of restricting the availability of harmful amounts of vitamin A to the misinformed and unsuspecting lay public in the hope of preventing this avoidable toxic disorder, as well as to publicize the widespread occurrence of this syndrome in mild and subclinical forms, and to plead for temperance on the part of practitioners in the administration of massive doses of vitamin A where its justification is questionable at best. As succinctly stated by Dickey and Bradley,[27] "the treatment (of hypervitaminosis A), both active and prophylactic, is obvious; the former a complete withdrawal, and the latter a sane and rational administration of vitamin A."

## CLINICAL DESCRIPTION

Chronic hypervitaminosis A is a clinical entity which is most frequently seen in late infancy and early childhood, although it is sporadically reported in adults. The pathological processes are attributable to a prolonged and excessive elevation of blood

vitamin A levels, and possibly in some cases to a disorder of vitamin A metabolism. The normal values for vitamin A blood levels are variously quoted as ranging from 50 I.U. to 150 I.U. per 100 ml. of serum. A level of 90 I.U. to 100 I.U./100 ml. (33 micrograms per cent is generally accepted as the average normal level.

Clinically, the condition in children is manifested by anorexia, loss of weight, extreme irritability and fretfulness, severe pruritus with or without a rash, alopecia, and sparseness and coarseness of the remaining hair. Concommitant with the development of these symptoms, or later, there may occur seborrhea-like cutaneous eruptions, fissuring at the corners of the mouth, cracking and bleeding of the lips, and palpable enlargement of the liver.

However, the most distressing symptom is the development of extremely painful swellings over the long bones. The pain is frequently severe enough to prevent sleep at night, and generally causes resistance to handling, protective limping, and even refusal to stand or walk on the part of the child.

Radiographic studies of the tender bony swellings show periosteal reactions, the so-called hyperostoses, greatest in width at or near the mid-shaft, and usually affecting multiple bones, particularly those not protected by a covering of heavy muscle layers. A history of prolonged and excessive vitamin A ingestion, an elevated plasma level of vitamin A, and a prompt clinical recovery following withdrawal of all vitamin A from the diet, complete the picture and confirm the diagnosis.

## HISTORY AND REVIEW OF THE LITERATURE

The effects of feeding supernormal doses of vitamin A to dogs and other animals was first noted by a group of Japanese investigators in 1925, but the results remained undiscovered in a Japanese journal[13] for the next several years. During the late 1920's and early 1930's, the first reports of toxic effects produced by vitamin A began to appear in European and American publications.

Domagk and von Dobeneck[14] found that when rats are given toxic doses of vitamin A (over 15,000 units per day), they lose weight almost immediately and may die in a week to ten days. There are certain rather constant symptoms; the hair, especially about the head, becomes unkempt and falls out, and the skin becomes greasy and has a peculiar odor. Later the eyes become sore, the lids become sealed, there is a bloody secretion from the nose, the liver becomes enlarged, and diarrhea develops. An almost constant

feature is the development of multiple spontaneous fractures of the bones of the extremities.

Concurrently, von Drigalski[15] was administering 0.5 and 1.0 cc. of a vitamin concentrate, "Vogan," (containing 40,000 units of vitamin A/cc.) to white rats daily. Within four to six days, these animals also showed dishevelled fur, marked loss of weight, and emaciation. After five to eight days, catarrhal symptoms such as conjunctivitis, haemorrhagic rhinitis, and diarrhea appeared, and by the nineteenth day, all the animals on both dosages were dead. Postmortem examination[15a] disclosed degeneration of the renal glomeruli and tubules, proliferation of the R.E. cells of the spleen, absence of striations in cardiac muscle fibres, degeneration of the testes, and only slight changes in the liver.

Within the same year, Collazo and Rodriguez[16, 16a] conducted similar experiments with rats. In addition to trophic changes of the skin and loss of hair, they noted cessation of growth, inflammatory changes of the eyes, bilateral exophthalmos, and spontaneous fractures. The lesions of the bones suggested osteomalacia, but could not be prevented by large doses of vitamin D. When, however, vitamin A was withdrawn, the fractures healed, and the animals recovered and gained weight. Similar changes were observed by Finucci,[17] and by Chalier and Jeune[18] in guinea pigs and other animals.

In their animals, Vedder and Rosenberg[19] found that the clinical symptoms of vitamin A poisoning agreed well with those seen by Collazo and Rodriguez[16a]—diminished growth curve, haemorrhages from the eyes and nose, exophthalmos, and rarefaction of bones with a pronounced tendency to spontaneous fractures. They concluded that the lesions reported by von Drigalski and Laubman[15a] were probably due to another toxic factor, in addition to vitamin A, that was present in the particular concentrate used in the latter's experiments. They remark that "the question as to the toxicity of large doses of vitamin A cannot be regarded as completely settled, and complete answer must await isolation of vitamin A in pure form." Furthermore, they surmised that it would probably require at least 100,000 units/day of the purified vitamin to produce toxic manifestations.

Another group of investigators led by Rossi[20] were unable to duplicate any of these effects in animals and, therefore, concluded that high doses of vitamin A were not toxic. However, Rossi's group made use of much lower daily dosages of vitamin A than had been suggested by Vedder and Rosenberg. Clausen,[9] in an

excellent review of the experimental work on the subject, came to the conclusion that "the literature is so contradictory at the present time (1938) as to afford no adequate evidence that vitamin A would have harmful effects for human beings."

The acute toxicity of polar bear liver to Arctic travellers, Eskimos, and their dogs, has long been common knowledge among peoples who frequent the far North. Rodahl and Moore[21] established that this toxicity is apparently due to the high content of vitamin A in this liver, which they found was approximately 18,000 units/gm. After feeding polar bear liver to rats, they estimated that if 100,000 units of vitamin A are sufficient to cause immediate illness in rats, then about 7.5 million units should cause acute illness in man. This amount would be present in about 400 gms. of bear liver, not an excessive portion for one meal. Several parties of Arctic explorers have been poisoned in this fashion, the most recent incidence being in 1940, and a number of deaths have been reported.[10a]

Rodahl and Moore then proceeded to produce experimental vitamin A toxicity in small animals, and observed a wide variety of toxic manifestations. 50,000 I.U. of vitamin A was administered daily to rats, as halibut liver oil. Almost invariably this caused skin lesions; roughening of the hair, alopecia, seborrhea, and peeling at the corners of the mouth. However, the most specific injury seemed to be softening and fractures of the long bones seen most frequently in growing rats, and profuse and sudden internal haemorrhage particularly under the skin and in the pericardium. These animals readily bled to death if cut on the paw. Ingestion of large amounts of polar bear liver produced identical lesions in rats; however, the residue of the liver after extraction of the vitamin A with alcohol could be fed in any amount without producting any ill effects.[21]

Wolbach,[22] in a classic paper in 1947, made comprehensive studies of the skeletal changes produced by excess vitamin A in animals. His histologic investigations in rats and guinea pigs indicated that all features of skeletal maturation are accelerated; there is a speeding up of the metabolism of epiphyseal cartilage cells, endochondral bone formation, and subperiosteal appositional growth of the cortex. The rapid and excessive tubulation of rat bones resulted in long bones of smaller caliber than normal, in contrast to the swollen thickened shafts which have been observed in the human examples of clinical vitamin A poisoning. Gribetz, Silverman, and Sobel[23] speculate that if patients with hyper-

vitaminosis A were to go undetected, and if the high dosages of vitamin A were to be continued for a sufficient length of time, destructive changes similar to those seen in animal experiments might occur.

It was Josephs[1] who first pointed out the dangers of abnormally high vitamin A dosage in pediatric practice, and who first demonstrated the value of the increased blood level of vitamin A in the diagnosis of chronic intoxication. He described hypervitaminosis A in a boy 34 months of age who had received one teaspoonful of halibut liver oil (240,000 USP units) daily after the third month of life, and who occasionally drank the oil directly from the bottle. Toomey and Morissette[24] observed deep, hard, tender swellings in the extremities and were the first to describe cortical thickening in tubular bones. Their patient was a boy 23 months of age who had received 250,000 units to 500,000 units daily of vitamin A since the second week of life.

After withdrawal of Oleum Percomorphum and subsidence of clinical signs, Toomey and Morissette reinduced the original signs and symptoms by refeeding calculated amounts of the preparation. In order to rule out the possibility of vitamin D being responsible, (also contained in Oleum Percomorphum, but only to the extent of 8500 USP units/gm.), the experiment was repeated, utilizing only pure vitamin A. This too caused a recurrence of the identical symptoms and signs as originally observed, and conclusively established the etiology of the syndrome beyond any doubt.

Dickey and Bradley[25] reported pruritus, hepatomegaly, and tender swelling and cortical hyperostoses in a child 22 months of age, who was poisoned by large amounts of cod liver oil and concentrates fed daily since early infancy (a total dosage of 400,000 units per day for at least 1½ years). Two patients of Rothman and Leon,[26] who were poisoned by excessive dosages of between 100,000 units and 200,000 units daily for thirteen and twenty-one months respectively, exhibited pruritus, sparse coarse hair, hepatomegaly, and painful extremities with cortical hyperostoses.

Cases now were reported with increasing frequency, and a total of ten cases were presented in the literature in the year of 1950, tripling the total number of recorded cases since the first report of a case in a human by Josephs.[1] Two of the cases were reported by Fried and Grand,[4] in children 16 and 24 months of age, who manifested extremely high blood levels of vitamin A, sparse coarse hair, generalized pruritus, hepatomegaly, and extremely tender

swellings of the extremities, which proved on radiologic examination to be due to subperiosteal elevations of the ulnae and tibiae. These children had been receiving 500,000 units and 180,000 units daily respectively of vitamin A as Oleum Percomorphum for many months.

Caffey,[5] in an important paper in 1950, carefully reported on the clinical manifestations, the roentgenographic changes in the skeleton, and the elevation of the blood vitamin A in a group of seven infants and young children chronically poisoned by ingestion of excessive amounts of vitamin A concentrates over periods of several months. Caffey's roentgenographic observations[5, 7] are far more complete and detailed than in any other reports. However, the morbid anatomy of the lesions in man continued to remain unknown, since there had been no biopsies nor necropsies up to that time. In addition, Caffey discussed in detail the differential features of vitamin A intoxication with those of infantile cortical hyperostosis, a syndrome with which hypervitaminosis A was, and probably still is confused.

In each of Caffey's seven cases, the clinical recovery was rapid and uneventful following complete withdrawal of the vitamin, with remission of all distressing symptoms in from four to twenty-two days. Caffey concludes that the excessive dosage was due to overenthusiasm for vitamins, and ignorance of the dangers of high vitamin intake, and cautions that "the hazards of vitamin A poisoning from the routine prophylactic feeding of vitamin concentrates A and D to healthy infants on good diets are considerably greater than the hazards of vitamin A deficiency in healthy infants and young children *not* fed vitamin concentrates."[6]

In 1951, Rineberg and Gross[27] presented a case in which a 33 month old child had received overdosages of vitamin A for about nine months. In this case the clinical picture could not be clearly differentiated from infantile cortical hyperostosis despite the valuable differential criteria already supplied by earlier authors. However, improvement was dramatic after cessation of vitamin A intake, which fact indisputably established the true etiology of the skeletal changes as vitamin A excess. This case is unique in being the first in which a successful surgical biopsy of a skeletal lesion had been performed. Microscopic examination revealed a strip of newly formed, poorly calcified subperiosteal bone of coarse fibred structure. The pathological diagnosis was "productive periostitis."

In the cases of chronic intoxication in infants described thus far, wide variations in the dosages of excess vitamin A were reported, ranging from 75,000 units to 600,000 units per day. The time lapse before the onset of toxic symptoms was one month at least, and six months on the average. Although vitamin D also was being administered in excess in many of these cases, there were no reports of concurrent vitamin D toxicity, and in fact, the role of vitamin D as a factor in the pathogenesis of this syndrome has been strongly refuted by a large number of investigators.[5, 23, 24, 25, 36, 46, 53]

Up to this time, all the cases reported had occurred in infants or young children. In 1951, Sulzberger and Lazar[28] presented the first report of a case in an adult. Despite the distinct differences in physiological, chemical, and general body economy of the adult, the general syndrome in their patient was basically similar to that previously reported in infants and children. However, several features of the syndrome which had never been described before in children were discussed: menstrual changes, absence of radiologic changes of the bones, and a chloasma-like pigmentation of the face. The effects and mechanisms of excess vitamin A on various organs and systems, and particularly on the keratin structures, also were discussed.

Since the Sulzberger and Lazar report, three additional cases of chronic hypervitaminosis A in adults have been reported.[29, 30, 31] Most recently, Gerber, Raab, and Sobel[31] have reported the case of a young woman who was admitted to six hospitals over a period of nine years before her illness finally was diagnosed as vitamin A toxicity. During this period she suffered from severe dermatologic lesions, increased intracranial pressure (for which a craniotomy was performed), crippling bone and joint pains, and a rigid "poker spine." To date, this patient is the only adult reported to demonstrate bony changes on radiologic examination, which consisted of extensive calcification of cartilaginous, ligamentous, tendinous, and subperiosteal structures.

Acute incidents may follow the administration of very large doses of vitamin A in the infant. These incidents are especially characterized by acute hydrocephalus with spontaneous and intensive bulging of the fontanel, frequent vomiting, agitation, and either insomnia or somnolence, all without any meningeal or neurological sign or systemic symptoms. The disturbances begin twelve hours after ingestion of the vitamin, and end twenty-four to forty-eight hours later either, spontaneously or after lumbar puncture.[54]

In May 1951, Marie and See[46] reported the first three cases of this acute syndrome (which now bears their names). By clinical experimentation, they demonstrated conclusively that vitamin A alone was responsible for the acute benign hydrocephalus, and succeeded in reproducing the syndrome in puppies by administration of massive doses of pure vitamin A.[84] More recently, pediatricians throughout Europe, particularly France and Spain, have reported veritable "epidemics" of this syndrome,[46-84] due no doubt to the ready availability of a preparation, "Vitadone Forte," containing in a single ampoule, 350,000 units of vitamin A.

In addition, case reports and discussions of chronic hypervitaminosis A have continued to be published in various journals with increasing frequency within the last few years.[27-41] In response to the renewed clinical interest in the syndrome, there has been a very active revival of activity in the experimental field, and recently, numerous reports of the effects of vitamin A toxicity in laboratory animals and on tissues in culture have appeared.[66-75] These promise to add greatly to our understanding of the pathogenesis and anatomical nature of the specific pathological lesions which are produced in tissues by excessive concentrations of vitamin A.

## DIFFERENTIAL DIAGNOSTIC FEATURES

The diagnosis of hypervitaminosis A depends on the following points:

1. Presenting symptoms of irritability, anorexia, pruritus, loss of hair, fissuring of the lips, mild hepatomegaly, and painful swellings of the extremities, producing protective limp or failure to bear weight. Constipation, failure to gain weight, and coarseness and sparseness of the remaining hair are frequently associated with the main symptoms.

2. Roentgenograms reveal subperiosteal new bone growth, and cortical thickening of the long bones, particularly the ulnae, fibulae, clavicles, and metatarsals (excluding the first).

3. The diagnosis is confirmed by eliciting a history of excessive vitamin A intake, and the finding of an elevated plasma vitamin A level.

4. Symptoms disappear rapidly when vitamin A intake is completely discontinued, but reappear if vitamin A is resumed before subsidence of blood levels and regression of anatomical changes is complete.

Several authors[5, 23] have stressed that the toxic symptoms of hypervitaminosis A seldom appear until after the first year of age, and never during the first four months of life. There are two plausible reasons for this; first, the absorption of even large amounts of oily preparations of vitamin A is very poor in the first few months of life, as shown by Sobel and coworkers.[56] Also, despite the early age at which some of the diagnoses have been made,[34, 35] there is nevertheless a very considerable latent period between the onset of excessive consumption of vitamin A, and the appearance of diagnostic clinical signs.[1, 5, 23, 24, 25, 26, 33] This latent period averages about six months, but has been considerably longer in a number of cases (between 1½ years and 3 years). Caffey[5] observed that the length of this latent period is not dependent on the magnitude of the overdosage. He used the appearance of tender swellings in the extremities as the criterion for dating the onset of the clinical disease. In a majority of cases, pruritus,

TABLE I. FREQUENCY OF SIGNS, SYMPTOMS, AND PERTINENT LABORATORY FINDINGS IN TWENTY-FIVE CASES OF CHRONIC HYPERVITAMINOSIS A

| *Signs and Symptoms* | *No. of Patients* | *% of Patients* |
|---|---|---|
| Onset after 6 months of age | 25 | 100% |
| Normal serum levels of Ca and P | 15 (out of 17) | 88% |
| Tender swollen extremities | 22 | 88% |
| Periosteal thickening of long bones | 21 | 84% |
| Irritability and fatiguability | 20 | 80% |
| Pruritus | 16 | 64% |
| Alopecia and sparse, coarse hair | 15 | 60% |
| Elevated alkaline phosphatase activity | 10 (out of 17) | 59% |
| Anorexia | 14 | 56% |
| Limp, or failure of weight-bearing | 13 | 52% |
| Fissuring and soreness of the lips | 12 | 48% |
| Desquamating rash | 10 | 40% |
| Hepatomegaly | 10 | 40% |
| Weight loss | 6 | 24% |
| Constipation | 5 | 20% |
| Craving for butter | 5 | 20% |

anorexia, and alopecia precede tender swellings by several weeks or months; however, anorexia and pruritus are so common in children who do not have vitamin A intoxication that the significance of their appearance in cases of vitamin A overdosage is

exceedingly difficult to evaluate from a diagnostic standpoint, unless bony changes are present as well.

Single case reports have mentioned other signs and symptoms, many of which are probably incidental, and not related to the main pathological process. These include: polydipsia, polyuria, melena, tachycardia, asthenia, splenomegaly, clubbing of the fingers and toes, hoarseness, photophobia, hyperreflexia, edema of the feet, edema of the face and eyelids, low grade fever, night sweats, depressed serum proteins, and leukopenia.

The description of chronic hypervitaminosis A in adults differs somewhat from the infantile form of the disorder, in the relative mildness of the bone pains, absence of radiographic changes (except for one case[31]), menstrual alterations, exophthalmos, and pigmentation of the skin. The skin and its appendages (hair and nails) are generally the most severely affected structures in adults. There are no significant alterations in alkaline phosphatase activity in adults, and palpable hepatomegaly is not as marked or as common as in children. Otherwise, intoxication in adults presents findings basically similar to the well characterized syndrome in children: listlessness, anorexia, weight loss, alopecia, pruritus, dermatitis, and tenderness over bones and joints.

The levels of vitamin A in the plasma have been markedly elevated in all patients with this syndrome whose blood has been analyzed. The concentrations almost always exceed 500 I.U./100 ml., and most commonly range between 800 and 2000 I.U./100 ml., with the highest reported value being 6660 I.U./100 ml.[31] It is not certain how early the blood vitamin A level rises, or whether it remains elevated during the long latent period prior to the appearance of clinical manifestations. It is possible, however, that an excess of vitamin A in the blood might point to the diagnosis while that patient was still asymptomatic or just had vague generalized complaints. This indicates the usefulness of a careful vitamin history in pediatric practice, and the routine questioning of adults for any unusual degree of vitamin consumption in this day and age of ritualistic vitamin dependency.

Following cessation of ingestion of excessive vitamin A (and in some cases, withdrawal of all carotene-rich foods is required as well), the vitamin A blood level immediately begins to fall, but soon tapers off, and only very gradually returns to normal levels. If at any time while the vitamin A level is still elevated (for several weeks to months after withdrawal), that is, while the liver stores are still saturated or supersaturated, ingestion of further vitamin A

will produce a prompt exacerbation of the previous symptoms.[5, 24, 28, 33, 35]

The rapid and complete clinical recovery of these patients after the cessation of vitamin A intake is one of the most dramatic and diagnostically convincing features of the syndrome. Pruritus, irritability, anorexia, swellings, limp, and bone pain completely disappear within the first three to ten days. Any lost weight is rapidly regained within two weeks or so. Hepatomegaly regresses completely in about three weeks. Recovery is so dramatic as to be worth comparing with the rapid and complete reversal of even the most severe manifestations of scurvy within a short period after the administration of ascorbic acid is begun.

In hypervitaminosis A, however, dystrophies of the keratin structures may be more stubborn, requiring about a month before new fine hairs begin growing in to replace the lost eyebrows, eyelashes, lanugo hairs, and scalp hair. In Sulzberger's case, ten weeks were required for reversion of the softened and brittle finger nails to normal. The most conspicuous residue, however, is the roentgenographic evidence of cortical hyperostoses which persist for many months despite the complete disappearance of bone pain, and regress only very slowly.[6, 23, 25, 31, 33, 35]

Hypervitaminosis A may be commonly confused with several other disorders, chief among them being the syndrome of infantile cortical hyperostosis, first described by Caffey and Silverman. Among the other disorders which have been entertained by various clinicians in the differential diagnosis are avitaminosis A, scurvy, hypothyroidism, Addison's disease, leukemia, rickets, acute periostitis, infectious arthritis, poliomyelitis, syphilis, rheumatic fever, and tuberculosis.

The first three of these merit careful consideration at least on the basis of morphological similarities; as for the others, the taking of a careful history and an alert physical examination and laboratory workup should very soon eliminate them as diagnostic possibilities, unless one or another should happen to coexist coincidentally with vitamin A toxicity. On the other hand, confusion of hypervitaminosis A with infantile cortical hyperostosis is not an infrequent diagnostic error, as observed by Caffey from his own experience with these two disease entities.[7a]

Actually, there are but two features which are common to both disorders—cortical hyperostoses, and tender soft tissue swellings. Though rigid differential criteria do not exist, there are certain preliminary distinguishing features which are present in infantile

cortical hyperostosis (hereafter referred to as ICH). These include:[5, 6, 7]

(1) Absence of a history of excessive vitamin A intake; (2) onset before six months of age—ICH almost always makes its appearance during the first four months of life, and in one case was present on the first day of life. In hypervitaminosis A, on the other hand, diagnostic clinical signs have been recognized only once or twice prior to the first birthday; (3) fever, accompanied by a high sedimentation rate and leukocytosis—fever is the rule in ICH (15 of 17 cases cited by Caffey); fever, other than transient elevations due to coincidental respiratory infection, is absent in chronic hypervitaminosis A; (4) occurrence of pleural effusions in many cases of ICH; (5) normal plasma vitamin A levels—the blood vitamin A level has been significantly elevated in hypervitaminosis A in every patient tested; blood vitamin A levels were normal in the patients with ICH so tested; (6) failure of improvement of symptoms if vitamin A is withdrawn or withheld—recovery from hypervitaminosis A is dramatically rapid after cessation of ingestion of vitamin A; in contrast, the signs and symptoms of ICH have continued, and exacerbations have occurred weeks and months after hospital entry, when it was certain that excessive ingestion of vitamin A had not been taking place.

Roentgenographically, there are several outstanding differences which pronounce the two disorders to be separate entities, according to Caffey.[5, 7]

1. Periosteal new bone formation is not markedly different qualitatively in the two conditions, although it is generally more profuse in ICH, and the edges of the hyperostoses are much rougher than their counterparts in hypervitaminosis A.

2. Soft tissue swellings in ICH are usually larger and more tender, and are frequently discolored as well.

3. In hypervitaminosis A, involvement of the ulnae and of all the metatarsals with the exception of the first, has been regularly noted. Metatarsal hyperostoses have been demonstrated in only one case of ICH.

4. Scapular lesions are practically unknown in chronic hypervitaminosis A; they have been present in several cases of ICH.

5. The face and jaw have been swollen, and the mandible thickened in every case of ICH; these structures have only been affected in a single case of hypervitaminosis A—in the case reported by

Rineberg and Gross,[27] the marked degree of periosteal thickening in the long bones, and the changes in the mandible and soft tissues were characteristic of ICH, and clinically, a distinction could not be made. However, there was a history of nine months of excessive vitamin A intake, the child was 33 months old, and improvement was dramatic after withdrawal of vitamin A from the diet, all proving conclusively that hypervitaminosis A and not ICH had been the underlying disease process.

(To be concluded in the May Issue.)

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MYASTHENIA GRAVIS: FOUR CASES. M. Latorre and R. Reynoso. (Rev. chilèna pediat., 26:471-476, Nov.-Dec. 1955).

Myasthenia gravis is very rare in children. Four cases were observed during the last six years in the Luis Calvo Mackenna Hospital of Santiago, Chile. The patients were three boys between the ages of 7 and 14 years and a 10-year-old girl. The symptoms in all patients were similar, consisting of extreme fatigability, especially in the morning, palpebral ptosis, lowering of the angles of the lips, difficulty in deglutition and in speech, strabismus, and facial paralysis. The symptoms were more severe in the course of infections. The prostigmine test was positive in all. Mental and sensory reactions were normal. A roentgen examination of the thorax for shadows of persistent thymus was made in two cases, with a positive result in one case and a negative result in the other. The treatment consisted of prostigmine by mouth in doses of 15 mg. every six hours up to a total daily dose of 60 mg. This dose was maintained for a certain time and then it was progressively diminished until its discontinuation in, as a rule, about a year. The symptoms were controlled in all patients but one. They reappeared in this patient two years after the cure. They were due to strenuous physical effort during sport and were permanently controlled by administration of prostigmine on the above schedule for a short time. One of the patients, after having experienced great improvement, developed acute respiratory disorders that did not respond to treatment. He died. Autopsy showed bronchopneumonia of the lower lobe of the left lung and diffuse hyperemia and hyperplasia of the thymus (thymus weighed 60 gm.) The other three patients were normal at the time of writing, from four to six years after the cure of the disease. —*J. A. M. A.*

# DEPARTMENT OF ABSTRACTS

*Conducted by*

MICHAEL A. BRESCIA, M.D., NEW YORK

CORIELL, L. L.; SCHAEFFER, K.; FELTON, H. M.; FERNANDEZ-MORAN, H. and BIERLY, M. Z., JR.: A SEROLOGIC AND CLINICAL SURVEY OF POLIOMYELITIS IN CARACAS, VENEZUELA AND GALVESTON, TEXAS, AND THE RESPONSE TO SALK VACCINE. (American Journal Public Health, 46:1431, Nov. 1956).

A serologic survey of antibodies for all three types of poliovirus in children from Caracas and Galveston showed that infection occurred in infancy in children who attended free medical clinics in each city. A group of children from families of the university staff in Galveston presented a very low incidence of naturally acquired antibody for all three polioviruses. A survey of clinical poliomyelitis in the two cities for the past ten years shows that 85 per cent of reported cases occur in children under four years of age in Caracas; whereas in Galveston there are two periods of peak incidence corresponding to early infancy and to later childhood and adulthood.

Evidence is presented that within the temperate zone, geography is of minor importance in determining the epidemiology of poliomyelitis and that personal hygiene and living standards are the significant factors. Administration of the Salk vaccine stimulated antibody formation in all groups of children, that is, those with or without a high percentage of naturally acquired antibody. The vaccine would, therefore, appear to be effective in those individuals who need it most because they have not experienced previous infection. AUTHORS' SUMMARY.

ZIMMERMAN, F. T.: EXPLOSIVE BEHAVIOR ANOMALIES IN CHILDREN ON AN EPILEPTIC BASIS. (New York State Journal of Medicine, 56:2537, Aug. 15, 1956).

Anticonvulsant medication was given to a group of 200 children having severe behavior disorders with the common characteristic of periodic, paroxysmal outburst of impulsive behavior which seemed imbedded in a matrix of generally bad behavior.

No frank convulsive seizures were noted in any case, but the EEGs of all of these children were abnormal and included features found among patients with generalized seizures. Results show improvement in behavior in 70 per cent of the cases treated with anticonvulsant medication, 25 per cent of the patients remained the same, and in 5 per cent, worse behavior was reported following therapy. EEGS improved in 50 per cent and Rorschach protocols in 55 per cent of the patients. The addition of an organic Rorschach initially in the majority of cases showing improvement, it is believed, provides valid evidence of a nonpsychogenic etiology. The presence of four positive factors—paroxysmal behavior, abnormal EEG, organic Rorschach, and definite improvement with the anticonvulsant drug Dilantin—warrants the inclusion of this group of children, it is believed, in the diagnostic category of epileptic equivalents. However, it seems that a distinction should be made between epileptic equivalent and psychomotor epilepsy, and evidence in this study points away from epileptic equivalent and psychomotor epilepsy being the same. EEG findings are more in line with what is often seen in grand mal and seem more in keeping with a frontal lobe origin. Finally, it is believed that thinking in epilepsy should be reoriented to the possibility that the phenomenon of the epileptic equivalent is not associated predominantly with adulthood but is more common in childhood than is generally realized. Author's Summary

SALK, J. E.: ANTIGENIC POTENCY OF POLIOMYELITIS VACCINE. (Journal American Medical Association, 162:1451, Dec. 15, 1956).

The amount of virus antigen injected is the principal determinant of the intensity of the immune response. This is reflected in the level of antibody induced and/or in the degree of immunologic hyperreactivity effected. Although antibody, at demonstrable levels, tends to persist for long periods, it has been observed that immunologic hyperreactivity continues, even in those cases in which antibody has declined to nonmeasurable levels. The indications are that immunity to paralysis is mediated not only through existing antibody in the circulating blood but also through the mechanism of immunologic hyperreactivity that calls forth antibody sufficiently rapidly, after exposure, to intercept invasion of the central nervous system even though pharyngeal or intestinal infection may have occurred. Author's Summary

SKATVEDT, M. and LUNDERVOLD, A.: THE SIGNIFICANCE OF ELECTRO-ENCEPHALOGRAPHIC SPIKE FOCI IN PATIENTS WITH CEREBRAL PALSY WITHOUT EPILEPTIC SEIZURES. (Acta Paediatrica, 45:440, July 1956).

The signifiance of spike foci in EEG in patients who have had no clinical epileptic seizures has been considered as questionable. Three cases are reported in which EEG showed spike foci 2 weeks, 5 weeks and 2½ years before the occurrence of the first clinical epileptic seizure. These observations indicate that spike foci shown in EEG represent an actual danger of later clinical epileptic seizures. Author's Summary

EMERY, J. L. AND CROWLEY, E. M.: CLINICAL HISTORIES OF INFANTS REPORTED TO CORONER AS CASES OF SUDDEN UNEXPECTED DEATH. (British Medical Journal, 5008:1518, Dec. 29, 1956).

In a series of 50 infants in which "sudden unexpected death" occurred, in only five instances was the history obtained by the coroner substantially consistent with the history obtained after the child's burial. Follow-up histories showed that all of the infants had shown some abnormality before death, and that the majority had had symptoms of over two days' duration. It is suggested that these inadequate histories are due to the psychic trauma of the unexpected death, together with the fear produced by the police and the coroner's investigation. The procedures connected with these infant deaths need revision. Author's Summary

GARAU, A.: STUDIES OF THE BLOOD LIPIDS IN CHILDREN WITH MEDITERRANEAN ANEMIA. (Annali Italiani Pediatria, 9:528, Dec. 1956).

The author studied the lipid fractions of the serum and whole blood of seven children with Mediterranean (Cooley's) anemia and found an increase in total lipemia, neutral fats, fatty acids and combined cholesterol and with a moderate reduction of the phospho-lipids. The author postulates that since these fatty changes have an effect on the osmotic mechanism of the globular membranes, these alternations might account for a primitive metabolic defect characteristic of Mediterranean disease. M.A.B.

FONTANA, V. J.; SPAIN, W. C. and DE SANCTIS, A. G.: THE ROLE OF ALLERGY IN NEPHROSIS. (New York State Journal of Medicine, 56:3907, Dec. 15, 1956).

In the study of 18 children with nephrosis, a positive familial history of allergy was elicited in approximately 66 per cent. In 44 per cent of the children, a positive history of personal allergy also was obtained. Evidence of "wheezing" was noted in 50 per cent of the children, either during a hospital admission or by the parents at home. Treatment of five cases with an antihistiminic drug resulted in the loss of weight in all patients, or a maintenance of weight while on therapy. These preliminary observations would seem to suggest an important relationship between allergy and the nephrotic syndrome. Authors' Summary

CORSA, L. JR.: CURRENT PREVENTIVE PROBLEMS OF CHILD HEALTH. (Journal American Medical Association, 161:1361, August 4, 1956).

In discussing the problems of child health, the author makes an elegant plea for breast feeding as follows: "I cannot leave the newborn infant without some mention of infant feeding—the natural kind. One important respect in which the U.S. differs from its sister nations is in the extent of breast feeding of its infants. The causes of the decline in function of the American breast to its present low ebb may never be clarified completely, but ranking high as contributing factors are the role of the American physician in devising and endorsing substitutes, the role of the American economy in mass-producing these substitutes, and the role of the American advertiser in equating the breast with sex. Despite many commercial attempts to imitate human breast milk, no substitute has been discovered that matches the natural product physiologically, in cost, or in ease of use. Rather, when we try too hard, we risk leaving out a vital factor, as in the recent epidemic of hypovitaminosis B6 resulting from modification of a manufactured formula. There are indications that the pendulum has completed its swing to the right and that an increasing number of young American mothers in the present generation want to, and probably will, nurse their babies. There is every reason for us as physicians to encourage rather than delay this healthy trend."

M.A.B.

# BOOK REVIEWS

*Conducted by*
MICHAEL A. BRESCIA, M.D., New York

ADVANCES IN PEDIATRICS. VOLUME IX. Edited by S. Z. Levine, M.D. Cloth. Pp. 336. Illustrated. Price $9.00. Chicago, Ill.: The Year Book Publishers, Inc., 1957.

This last in a series of "Advances" contains as usual some excellent articles. The treatment of the subject matter is fairly complete. Some of the subjects deal with matter that only recently has become prominent in the literature, and some of them are reviews of "old" subjects. The articles in this volume are as follows: Postmaturity by S. H. Clifford; The Gamma Globulins by C. A. Janeway and D. Gitlin; Thyroid Disorders in Childhood by W. A. Reilly; Familial Dysautonomia by C. M. Riley; Use of Fluoride Compounds in Prevention of Dental Caries by E. R. Schlesinger and D. B. Ast; Coagulation Disorders in Infancy and Childhood by I. Schulman and C. H. Smith; and Celiac Disease by H. A. Weljers, J. H. Van De Kamer and W. K. Dicke.

M.A.B.

ADRENAL FUNCTION IN INFANTS AND CHILDREN. A SYMPOSIUM. Edited by Lytt I. Gardner, M.D. Cloth. Pp. 221. Illustrated. Price $6.75. New York: Grune & Stratton, Inc., 1956.

The material in this book is based in large part on a symposium on adrenal function in infants and children held November 1954 under the auspices of the Department of Pediatrics, the State University of New York, Upstate Medical Center, Syracuse, New York. There are many studies incorporated in this symposium both fundamental and clinical. Under the former heading is a report by Helen W. Deane on the Histopathology of the Adrenal Cortex in Fetal and Prepuberal Rats. Among the clinical studies there are two articles which deserve special mention, viz: The Influence of Testosterone and Cortisone on Growth by Edna H. Sobel, and Blood ACTH and 17-Hydroxycorticosteroids in Children, with Special Reference to Rheumatic Fever by Vincent C. Kelley. There is much valuable information in this small volume.

M.A.B.

PSYCHOPATHOLOGY OF CHILDHOOD. Edited by Paul H. Hoch, M.D. and Joseph Zubin, Ph.D. Cloth. Pp. 303. Price $6.00. New York: Grune & Stratton, Inc., 1955.

This book comprises some sixteen papers with discussions by as many authors which formed the essential part of the 44th Annual Meeting of the American Psychopathological Association held in New York City in June 1954. These papers contain much valuable information and certainly would be rewarding to anyone interested in the psychological and psychiatrical aspects of infant and child problems. In the paper on Adolescent Frustrations and Evasions by Lawson G. Lowrey, he highlights one of many problems which beset this field, viz: "It is a fair estimate that no school system in the country provides adequately for the needs of approximately 20 per cent who do not profit from an academic curriculum beyond (at most) the 8th grade, but who could realize considerable potential through motor-manual and trade training. Discontent with school, increased restlessness, greater feelings of inadequacy, truancy, intensified hostility unleashed on the community—these are in the train of consequences". M.A.B.

PICA. By Marcia Cooper, Sc.D. Cloth. Pp. 114. Price $3.75. Springfield, Ill.: Charles C. Thomas, 1957.

This small volume is a concise review of pica from antiquity to the present day. Most of the material in the book has been culled from the literature. The author develops the theme that the etiology of pica is mainly a search of the body for elements deficient in the diet. Hence the common practice of ingesting dirt by primitive peoples, the American Negro slaves in the antebellum days, and by others on a markedly deficient diet. The book is interesting and easy reading. M.A.B.

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